SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

FEBRUARY 5, 2001

Gaithersburg Marriott
9751 Washingtonian Boulevard
Gaithersburg, MD

Circulatory System Devices Advisory Panel Meeting
February 5, 2001

Attendees

Acting Chairperson
Cynthia M. Tracy, M.D.
Georgetown University Hospital

Executive Secretary
Megan Moynahan
Food and Drug Administration

Voting Members
Salim Aziz, M.D.
University of Colorado

Michael D. Crittenden, M.D.
Harvard University

Warren K. Laskey, M.D.
University of Maryland School of Medicine

Consultants
Michael Domanksi, M.D.
NHLBI

Mitchell W. Krucoff, M.D.
Duke University Medical Center

George W. Vetrovec, M.D.
Medical College of Virginia

Francis J. Klocke, M.D.
Northwestern University Medical School

David L. DeMets, Ph.D.
University of Wisconsin, Madison

Consumer Representative
Robert A. Dacey

Industry Representative
Gary Jarvis
St. Jude Medical

Food and Drug Administration
James E. Dillard III
Stuart M. Portnoy, M.D.
Chris M. Sloan
Suzanne Kaiser
Gary Kamer
Paul L. Chandeysson, M.D.
Bram Zuckerman, M.D.
John E. Stuhlmuller, M.D.

CALL TO ORDER

Acting Chairperson Cynthia Tracy, M.D., called the meeting to order at 8:09 a.m. and asked the panel members to introduce themselves. Executive Secretary Megan Moynahan read the conflict-of-interest statement, noting that because of his status as a special government employee, panel consultant Mitchell Krucoff, M.D., could not participate in the morning panel deliberations. Dr. Tracy, Warren Laskey, M.D., George Vetrovec, M.D., and David DeMets, Ph.D., had received conflict-of-interest waivers and could participate fully in all discussions. Dr. Krucoff could participate fully in all afternoon discussions.

James Dillard, director of the Division of Cardiovascular and Respiratory Devices (DCRD), announced that Dr. Laskey and Salim Aziz, M.D., had been appointed to serve 4-year terms and that Dr. Tracy had been appointed chair of the panel for the duration of her term.

OPEN PUBLIC HEARING

No comments were made.

SPONSOR PRESENTATION: PERCUSURGE/MEDTRONIC

Dennis Wahr, M.D., St. Joseph Mercy Hospital, presented an overview of the PercuSurge GuardWire System as used in the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) Trial. He described why it is important to develop successful surgical intervention techniques for deteriorating saphenous vein grafts (SVG's) and explained how the PercuSurge GuardWire System works.

Donald S. Baim, M.D., Brigham & Women's Hospital, provided more details on the SAFER Trial design and outcome. He noted that an important component of the PercuSurge system is that it enables aspiration of embolic particles dislodged during angioplasty, thereby reducing the rate of major adverse clinical events (MACE). He explained that the inclusion criteria for the SAFER trial had to be expanded early in the study because enrollment was too

slow; this expansion was done in consultation with FDA's Data Safety and Monitoring Board. Ultimately, the study enrolled 142 patients under the original criteria (the RCT*-1 group) and 659 patients under the expanded criteria (the RCT-2 group), for a total of 801 patients. SAFER Trial results indicated that patients who received angioplasty with the PercuSurge device had a significantly lower rate of MACE than did patients who had the procedure with the control device. Dr. Baim presented additional study data supporting the efficacy of the PercuSurge device.

Richard Kuntz, M.D., Brigham and Women's Hospital, presented information on the statistical techniques used to analyze the results of the SAFER Trial. Expanding the inclusion criteria created some analytical challenges, and Dr. Kuntz described ways in which the sample of 801 was divided into separate cohorts and analyzed. Dr. Kuntz concluded that the RCT-2 group best represents patients with vein graft disease and therefore provides the best data set for estimating the MACE differences between the treatment and control groups.

Dr. Wahr then presented data on the actual use of the PercuSurge system. He described how physicians were trained to use the device, how device malfunction was defined, and what the malfunction rates were. He noted that improvements made to the PercuSurge device part way through the study reduced the malfunction rate.

FDA PRESENTATION

Suzanne Kaiser, biomedical engineer, Interventional Cardiology Devices Branch, Office of Device Evaluation, and lead reviewer for the PercuSurge system, summarized the nonclinical tests conducted on the PercuSurge system and discussed the results of the clinical investigation of the device. She said that the animal, bench, and biocompatibility testing demonstrate the

* RCT=Randomized Controlled Trial.

integrity and functionality of the device for its intended use, although issues related to the shelf life of the device and its packaging remain to be addressed with the sponsor. She noted that the incidence of device failures and malfunctions during clinical use of the system appeared to be high and that FDA is continuing to work with the sponsor to address the issue.

Paul Chandeysson, M.D., medical officer, Peripheral Vascular Devices Branch, DCRD, provided an overview of the SAFER trial design and summarized the results. He suggested some possible reasons for the apparent difference in the RCT-1 and RCT-2 groups and noted that differences in lesion characteristics between the two groups may have affected outcomes.

OPEN COMMITTEE DISCUSSION

Dr. Laskey noted that to truly examine efficacy, it is important to look at procedural risk as well as 30-day and 1-year MACE rates. He added that it would have been helpful to have data on graft ages and characteristics of the lesions in the SAFER study participants. Finally, Dr. Laskey said that the data from the RCT-2 group "carries the day." He asked for clarification on the use of MACE as an endpoint; on whether the presence of calcification is actually a marker for some other characteristic; on the relationship between device malfunction and MACE rates; and on the study's use of creatine kinase (CK) as a surrogate marker. Drs. Kuntz and Baim answered his questions to his satisfaction.

Michael Crittenden, M.D., asked Dr. Wahr whether anyone had looked at operator-specific outcomes; Dr. Wahr responded that although the data had not been specifically tracked, anecdotal evidence is that it takes operators three or four cases to become comfortable with the device. Dr. Crittenden asked whether any graft-specific data were available, and Dr. Kuntz replied that most grafts were more than 6 or 7 years old. Finally, Dr. Crittenden asked what would be considered a high rate of device malfunction, and Mr. Dillard replied that the FDA

considers a rate of more than 30 percent to be “not small.” Deborah Hinman, MSc., PercuSurge, pointed out that after the device was modified, failure rates declined.

Michael Domanksi, M.D., noted that for CK levels to be effective as a surrogate marker, they would have to have some relationship to mortality; however, the trial was not powered to look at mortality. Dr. Kuntz elaborated on the role of CK levels as a marker in the study and described the use of left ventricle dysfunction as an indicator of mortality risk.

Francis Klocke, M.D., pointed out that the MACE rates in the roll-in portion of the study suggest the influence of a learning curve, and he questioned how enthusiastically the device should be recommended for lower risk patients. Dr. Bain agreed that it is not surprising that the rate of complications was higher for people just learning to use the device. Dr. Wahr pointed out that at least two-thirds of the roll-ins were high-risk patients.

Dr. DeMets asked the sponsor questions about the statistical methodology of the SAFER Trial analysis, which Dr. Kuntz attempted to answer. Dr. DeMets stated that he rejected the notion of two trials (i.e., RCT-1 and RCT-2) and instead saw the study as one trial with subgroups.

Panel members asked the sponsor to clarify matters concerning the training process for the device, the use of the device in animal models, the use of CK rather than troponin as an indicator, and whether the device could be used on sequential vein grafts. Dr. Wahr responded to their questions to their satisfaction. Panelists asked questions concerning the second indication for use listed in the draft labeling, but Ms. Hinman explained that it was based on predicates in the literature and was not related to the SAFER Trial. The panel then turned to the FDA’s questions.

Question 1. Please discuss whether there are any substantial differences in the lesions treated in RCT-1 and RCT-2 that could affect the poolability of the data.
The panel generally agreed that data on the lesions in the two groups could be pooled

Question 2. A substantial difference in 30-day MACE rates was noted in the control arm of the SAFER Trial after inclusion/exclusion criteria were modified. . . . Please comment on this difference in control results. Are there any other methods that should be used to assess interventional risk in a diseased SVG graft?
The panel concurred that the age of the graft is an important consideration in assessing risk. Dr. Laskey added that the clinical characteristics of the lesions are important and that one would need to look at more than CK cutoffs.

Question 3. Considering both the planned a priori and realized post hoc interim looks at these data, do you have any recommendations regarding the following questions:

- **Please discuss the Type I error values that should be associated with each planned or realized look. These values must assure an overall study Type I error of 0.05. Their values may not only impact the results of hypotheses tests but may also change the widths of the reported confidence intervals. These changes could influence the evaluation process and the labeling.**
- **Please discuss whether the 142 patients enrolled prior to the change in the inclusion criteria should be included in the primary analysis. If not, which patient cohort should be the primary analysis cohort?**

Dr. DeMets referenced his earlier remarks and reiterated that he would focus on the entire study sample of 801 patients; the RCT-1 group is basically an interesting subgroup. He thought it made sense to adjust the P value, but not the confidence interval. The panel concurred with his comments.

Question 4. Please discuss the clinical importance of the device failure and malfunction events in the evaluation of the safety and effectiveness of the GuardWire System.
The panel concurred that the high device failure rate was cause for concern and that it was reasonable to ask for additional modifications to the device.

Question 5. Based on the data submitted by the applicant please discuss whether the benefits of the distal protection device in this patient population outweigh the risks associated with the use of this device.
The panel concurred that the benefits of the device outweigh the risks.

Question 6. One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the products potential adverse events, and explain how the product should be used to maximize benefits and minimize adverse effects. Please address the following questions regarding the product labeling (Section 2):

6a. Based on the data from RCT-1 and RCT-2 as discussed in question 2, do you recommend that the PercuSurge device be labeled for use in all SVG lesions? Please comment on the INDICATIONS FOR USE section (page 2) as to whether it identifies the appropriate patient population for treatment with the device.
Dr. Tracy suggested that the data would support using the device in all types of SVG's until a better way to identify lesions is developed. Dr. Laskey noted that the device is not suitable for use with ostial lesions and that the warning should be repeated in the labeling.

6b. Please comment on the CONTRAINDICATIONS as to whether there are conditions under which the device should not be used because the risk of use clearly outweighs any possible benefit.
The panel suggested no contraindications.

6c. Please comment on the WARNINGS and PRECAUTIONS sections as to whether it identifies all potential hazards regarding device use.
Dr. Tracy noted that the sponsor had pointed out that elevated CK levels were linked with increased mortality; she suggested that MI could be listed as an adverse event. The panel concurred that information on the need for special training in the use of the device should be included.

6d. Please discuss whether any improvements could be made to the labeling to help minimize the occurrence of device failures and malfunctions as discussed under question 4.
Dr. Tracy noted that this issue had been covered in the panel's earlier discussion.

6e. Please comment on the remainder of the device labeling as to whether it adequately describes how the device should be used to maximize benefits and minimize adverse events.
The panel had no additional comments.

6f. Do you have any other recommendations regarding the labeling of the device?
The panel had no additional recommendations in response to the question.

Question 7a. Please discuss any improvements that could be made to the training program to help minimize the occurrence of device failures and malfunctions as discussed under question 4.

Dr. Tracy suggested that sequencing training as the sponsor had described earlier—training a primary operator, who in turn trains those assisting him or her—was a rational approach. The panel concurred. Dr. Baim noted that the company's policy is to not sell the device to any facility unless it has an operator who has used the device in at least five cases.

Question 7b. Please identify any other important elements that should be contained in a physicians training program for this device.

The panel had no additional comments.

OPEN DISCUSSION: CLINICAL STUDY DESIGN ISSUES FOR DISTAL PROTECTION DEVICES USED IN SVG DISEASE

Dr. Kuntz discussed some of the problems with conventional RCT methodology, including the length of time required to obtain results and the ethical dilemmas that arise when early results indicate significant benefit from the experimental device. He described a new statistical methodology that enabled conventional RCT's to be converted to equivalence trials should early results warrant it. Committee members expressed interest in his idea.

Dr. Baim waived his presentation.

Dr. Wahr presented information on the differences between occlusion technology and filter technology. He noted that occlusion technology enabled a greater quantity of particles to be removed than did filter technology.

Michael Gibson, M.D., UCSF Medical Center, talked about the use of GP IIb/IIIa inhibitors in angioplasty. He described a study that compared Tirofiban and Abciximab, which found that the latter drug produced superior outcomes, using death and MI as endpoints. Dr. Gibson suggested that drugs that have similar mechanisms of action and which appear to be

equivalent may actually differ when tested “head to head.” He suggested that additional trials involving GP IIb/IIIa inhibitors in angioplasty might be warranted.

Ms. Hinman discussed the considerations that should be examined to protect the public health in the study of distal protection devices in SVG’s. She concluded that in light of the treatment effect of the SAFER trial, the technical differences between the GuardWire and other designs, the new nature of vein graft intervention, the regulatory history of approval of interventional cardiology devices, and the lack of obvious public health need, other distal protection devices should be randomized against PercuSurge’s GuardWire or standard medical practice. Panel members asked questions concerning the nature of possible trials and PercuSurge’s involvement in those trials. Dr. Krucoff urged that PercuSurge allow data from the SAFER trial to be used as a historic control for an equivalency-style registry.

Julie Broderick, Kensey Nash Corporation, noted that technology is changing rapidly, presenting challenges for those conducting clinical trials. She requested that the panel give serious consideration to the hybrid study design described by Dr. Kuntz that morning.

Gregg Stone, M.D., Lenox Hill Heart and Vascular Institute, provided background information on pathways to regulatory approval for distal protection devices in treating SVG’s and discussed advantages and disadvantages of RCT’s and registry approaches. He offered three conclusions: (1) After the PercuSurge device becomes clinically available, it will no longer be ethically justifiable to complete superiority trials involving distal filter devices. (2) Registry approval pathways will be undermined, unacceptable so, by a control selection bias, confounders, and the lack of an adequate equivalency database. (3) A noninferiority trial comparing a new device with the GuardWire, randomized with approximately 800 patients (the size of the SAFER trial) and using a 510k approval pathway (in case the study did show equivalence) to expedite its

arrival on the U.S. market after panel review, would provide important efficacy data. The process would be safer to the public, less burdensome, and fairer to the industry.

Jim Gustafson, vice president, Quality Systems and Regulatory/Clinical Affairs, Possis Medical, gave a presentation on clinical trials for distal protection devices in SVG's. He described the AngioJet Thrombectomy Catheter System, a device that is undergoing IDE clinical trial for ischemic stroke. He described the preliminary results of the trial, noting that one of the benefits of the AngioJet is that it actively dislodges and removes potentially embolic material prior to treatment; other types of distal protection devices generally evacuate the debris following treatment. He summarized by saying that any FDA guidance for clinical trials of distal protection devices should accommodate, among other considerations, patient selection, endpoint, and control implications of device design and treatment strategy to ensure that the results properly serve and inform both practitioners and the public.

Jerry Mezger, CEO and president, EndiCor Medical, described the X-SIZER Catheter System, a mechanical thrombectomy device for native vessels and SVG's to prevent distal embolization. He described the preliminary results of clinical trials with the device and highlighted some study enrollment issues, including participation at key sites and biased lesion selection in randomized patients. He concluded by saying that "in the post-PercuSurge era, historical MACE rates may be the only valid standard for comparison" and asked the panel to take the issues he raised into account in evaluating EndiCor's ongoing RCT.

William O'Neil, M.D., director of cardiology, William Beaumont Hospital, reiterated other speakers' concerns about the feasibility of and ethical issues involving RCT's for approving distal protection devices. He urged the panel to consider registries or noninferiority trials. He added that although the device in the SAFER trial could be improved upon, the

question remains of how to get promising devices on the market in a timely fashion. It is critical for the panel to consider the mode of failure in considering failure rates.

Stuart Kim, attorney, McKenna & Cuneo, Washington, DC, asked that the panel discuss, if possible, what unique measures (if any) should be included in the clinical study design of a proximal protection device for SVG disease. The panel chose not to discuss Mr. Kim's query because it did not fit with the agenda, time was limited, and the question was not clear.

FDA PRESENTATION

Bram Zuckerman, M.D., F.A.C.C., medical officer, DCRD, presented information on trial design issues associated with evaluation of distal protection devices in diseased SVG's. He pointed out that although percutaneous coronary treatment of SVG disease is often a preferred treatment strategy, a wide range of procedure success and complication rates has been reported for such procedures. Part of the variability can be explained (e.g., graft age, lesion length), but other factors are unknown. He said that development of safe and effective distal protection devices is an important research area in interventional cardiology; key issues in evaluation of those devices in diseased SVG's involve control groups, study endpoints, and study protocol. He noted that MACE is a composite endpoint.

PANEL DISCUSSION

The panel moved directly to consideration of the FDA's questions.

Question 1a: Given our current understanding of vein graft disease, please discuss the need for a randomized trial design when evaluating a new distal protection device for SVG use. When is a randomized trial necessary to ensure comparison to an appropriate control group?

The panel had mixed views on this question. Dr. Crittenden stated that an RCT was always necessary, whereas Dr. Domanksi suggested that a general rule was not possible. He added that for new concepts and designs, one cannot always use historical data. Dr. Tracy raised the issue of

how to define the appropriate control group. Dr. Krucoff said that the answer to the question was a “life cycle” issue and would vary.

Question 1b: Please discuss whether adequate trials can be designed with historical controls or objective performance criteria for assessment of this technology.
Dr. Dillard commented that the panel had answered the question in its discussion of Question 1a.

Question 1c: If a randomized trial is warranted, please discuss whether the control arm should incorporate use of an approved distal protection device. If so, please discuss use of an equivalence hypotheses, rather than a superiority hypothesis, for this study.
The panel concurred that the appropriate control is the standard of practice. Dr. DeMets suggested that the question of equivalence versus superiority hypotheses was not an either/or proposition and was not necessarily a good way of looking at the issue. The panel raised issues of determining and obtaining the appropriate sample size for controlled trials. Members also noted that centers’ differing standards of care affect studies. Dr. Domanksi suggested that new devices should be tested by people using the best standard of care. Dr. Laskey pointed out that the more an operator uses a device, the better the results are; studying actual device use is a moving target.

Question 2: Please discuss use of the 30-day MACE rate as the primary endpoint in a SVG distal protection device trial. Please discuss whether use of this composite endpoint captures important clinical events. Please discuss whether an in-hospital or 14-day MACE rate would be acceptable as a primary endpoint. Please discuss any alternatives to MACE that would be important to consider.
Dr. Tracy said that the lack of definition of high-risk vessels had to be addressed. Dr. Krucoff indicated that he thought the 30-day MACE rate was appropriate and that he would be concerned about using a 14-day rate. Dr. Laskey asked whether the FDA was concerned about safety or effectiveness and emphasized that MACE is a safety endpoint. He asked whether other endpoints—such as those beyond 30 days—should be included. Mr. Dillard acknowledged that the area was a complex one and that MACE has been treated as a catchall endpoint. Dr. Tracy

noted that the device design changed part way through the SAFER study and that one endpoint component would be device failure.

Question 3: Please discuss what secondary endpoints should be emphasized in a SVG distal protection device trial. For example, should a pathological description of the type and amount of debris removed by the device be included?

Panelists had a variety of suggestions, including the different components of MACE; device-related elements, such as ease of use, device failure, and secondary interventions due to the device; and effect on patient quality of life (QOL). Panelists were in general agreement that although it is difficult to capture, QOL is an important measure. Dr. Laskey suggested that QOL could be a postmarket measure.

Question 4: Please comment on appropriate entry criteria for a SVG trial that is intended to evaluate a new distal protection device. Please discuss any specific patient populations that should be excluded or studied separately.

The panel concurred that any SVG disease constitutes appropriate entry criteria. Dr. Vetrovec suggested that clot volume and relative flow at the outset could be a factor.

Question 5: Please comment on use of adjunctive antithrombotic medications. Please discuss, for example, whether glycoprotein IIb/IIIa drug use should be left to operator discretion or be prospectively outlined in the protocol.

The panel concurred that it was not appropriate to outline the use of GP IIb/IIIa at this point. Dr. Krucoff suggested that it was another heterogeneous standard-of-care issue and that it would be better for the FDA to focus on randomization and other issues. Dr. Laskey suggested that diabetics should be studied separately because they have different outcomes.

ADJOURNMENT

Dr. Tracy adjourned the open public hearing at 3:22 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on February 5, 2001, and that these minutes accurately reflect what transpired.

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Megan Moynahan
Executive Secretary

I approve the minutes of this meeting
As recorded in this summary.

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Cynthia M. Tracy, M.D.
Chairperson

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